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Metabotropic glutamate receptors in GtoPdb v.2023.1

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Abstract

Metabotropic glutamate (mGlu) receptors (**nomenclature as agreed by the NC-IUPHAR Subcommittee on Metabotropic Glutamate Receptors [351]**) are a family of G protein-coupled receptors activated by the neurotransmitter glutamate [140]. The mGlu family is composed of eight members (named mGlu1 to $mGlu_8$) which are divided in three groups based on similarities of agonist pharmacology, primary sequence and G protein coupling to effector: Group-I ($mGlu_1$ and $mGlu_5$), Group-II ($mGlu_2$ and $mGlu_3$) and Group-III ($mGlu_4$, $mGlu_6$, $mGlu_7$ and $mGlu_8$) (see Further reading).

Structurally, mGlu are composed of three juxtaposed domains: a core G protein-activating seven-transmembrane domain (TM), common to all GPCRs, is linked *via* a rigid cysteine-rich domain (CRD) to the Venus Flytrap domain (VFTD), a large bi-lobed extracellular domain where glutamate binds. mGlu form constitutive dimers, cross-linked by a disulfide bridge. The structures of the VFTD of $mGlu_1$, $mGlu_2$, $mGlu_3$, $mGlu_5$ and $mGlu_7$ have been solved [200, 275, 268, 403]. The structure of the 7 transmembrane (TM) domains of both mGlu1 and mGlu5 have been solved, and confirm a general helical organisation similar to that of other GPCRs, although the helices appear more compacted [88, 433, 62]. Recent advances in cryo-electron microscopy have provided structures of full-length mGlu receptor homodimers [217, 191] and heterodimers [91]. Studies have revealed the possible formation of heterodimers between either group-I receptors, or within and between group-II and -III receptors [89]. First characterised in transfected cells, co-localisation and specific pharmacological properties suggest the existence of such heterodimers in the brain [270, 440, 145, 283, 259, 218]. Beyond heteromerisation with other mGlu receptor subtypes, increasing evidence

suggests mGlu receptors form heteromers and larger order complexes with class A GPCRs (reviewed in [140]).

The endogenous ligands of mGlu are L-glutamic acid, L-serine-O-phosphate, N-acetylaspartylglutamate (NAAG) and L-cysteine sulphinic acid. Group-I mGlu receptors may be activated by 3,5-DHPG and (*S*)-3HPG [30] and antagonised by (S)-hexylhomoibotenic acid [235]. Group-II mGlu receptors may be activated by LY389795 [269], LY379268 [269], eglumegad [354, 434], DCG-IV and (2*R*,3*R*)-APDC [355], and antagonised by eGlu [170] and LY307452 [425, 105]. Group-III mGlu receptors may be activated by L-AP4 and (*R*,*S*)-4-PPG [130]. An example of an antagonist selective for mGlu receptors is LY341495, which blocks $mGlu_2$ and $mGlu_3$ at low nanomolar concentrations, $mGlu_8$ at high nanomolar concentrations, and $mGlu_4$, $mGlu_5$, and $mGlu_7$ in the micromolar range [185]. In addition to orthosteric ligands that directly interact with the glutamate recognition site, allosteric modulators that bind within the TM domain have been described. Negative allosteric modulators are listed separately. The positive allosteric modulators most often act as 'potentiators' of an orthosteric agonist response, without significantly activating the receptor in the absence of agonist.

Contents

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Introduction to Metabotropic glutamate receptors
https://www.guidetopharmacology.org/GRAC/FamilyIntroductionForward?familyId=40

Receptors

- $mGlu_1$ receptor
  https://www.guidetopharmacology.org/GRAC/ObjectDisplayForward?objectId=289
- $mGlu_2$ receptor
  https://www.guidetopharmacology.org/GRAC/ObjectDisplayForward?objectId=290
- $mGlu_3$ receptor
  https://www.guidetopharmacology.org/GRAC/ObjectDisplayForward?objectId=291
- $mGlu_4$ receptor
  https://www.guidetopharmacology.org/GRAC/ObjectDisplayForward?objectId=292
- $mGlu_5$ receptor
  https://www.guidetopharmacology.org/GRAC/ObjectDisplayForward?objectId=293
- $mGlu_6$ receptor
  https://www.guidetopharmacology.org/GRAC/ObjectDisplayForward?objectId=294
- $mGlu_7$ receptor
  https://www.guidetopharmacology.org/GRAC/ObjectDisplayForward?objectId=295
- $mGlu_8$ receptor

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